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MT–45: A NEW, DANGEROUS LEGAL HIGH

To the Editor:

Epidemiological data confirm that the use of new psychoactive substances is on the rise around the world.[1] Numerous reports have described medical emergencies associated with the consumption of unconventional drugs of misuse bought in "head" or "smart" shops or online.[1] New psychoactive substances, also referred as "legal highs," "smart drugs," or "research chemicals," are a large group of both plant derivatives and synthetic compounds, also in combination, purposefully designed as legal alternatives to illicit substances of abuse. The most popular and widely-spread new psychoactive substances are synthetic cannabinoids and synthetic cathinones, however, various different compounds such as amphetamine-like molecules, arylcyclohexylamines, synthetic hallucinogens, prescription drugs and hormones have been found in recreational products marketed as legal highs.[1]

In 2013, a study of Kikura-Hanajiri and colleagues performed on recreational products marketed in Japan after the introduction of generic scheduling of synthetic cannabinoids, revealed the presence of new types of psychoactive substances as MT-45 and AH-7921, never found before.[2] In 2014, the Swedish National Focal Point has signaled the presence of MT-45 in biological samples of 11 men deceased after consumption of recreational substances. Furthermore, still in Sweden, MT-45 was analytically confirmed in biological samples of two cases of acute intoxication and in a person suspected of a crime. In particular, MT-45 femoral blood concentration in the 11 deceased ranged between 0.33 and 1.9 μg/kg, and the substance was associated with other drugs of abuse. The Swedish National Board of Forensic Medicine concluded that in one case, MT-45 was the cause of death (femoral blood concentration of 1.9 μg/kg).[3] MT-45, IUPAC name 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, is a piperazine derivative with a molecular weight of 348.52428 g/mol. Currently, it is available as a research chemical only.

Analgesic activity evaluated in mice by the tail-pinch method via subcutaneous and intraventricular dose of MT-45 isomers showed that S(+) enantiomer and racemate were more potent than morphine, while R(-) isomer displayed weak activity. Naloxone stereospecific binding assay showed that S(+) enantiomer was more active than racemate, while in morphine stereospecific binding assay the results were opposed. Hill's coefficient was 1.21, 0.56, 0.78 and 1.22 for R(-) isomer, S(+) isomer, racemate and morphine, respectively. These results suggested that R(-) enantiomer and morphine interacted with opiate receptors in a similar mode, while S(+) isomer acted in a different manner.[4]

A study performed on both mice and rats showed that the activity of S(+) isomer was slightly more potent than that of racemate. Differently, it was highly more potent than that of R(-) isomer. In rabbits, racemate and S(+) isomer produced a negligible hyperglycemic and miotic effect.[5] Additionally, preclinical studies also highlighted the potential abuse liability of S(+) isomer.[6] In this regard, structure-activity studies suggested that the nitrogen at 4 position played a key role in determining the morphine-like effect of MT-45.[7]

In conclusion, MT-45 is a little-known substance and no study has evaluated its pharmacological and toxicological properties in humans. Preclinical studies have demonstrated that this piperazine derivative exerts an analgesic activity more potent than that of morphine. Unlike morphine, it produces a low miotic effect and this particular could cause misdiagnosis compromising the pharmacological treatment that is based on opioid antagonists such as naloxone. In addition, recent evidence suggest that recreational products currently available contain a combination of MT-45 and A-834735, 5-fluoro-PB-22, 4-methylbuphdrine and 4-methoxy-alpha-PVP increasing the risk of severe side effects.[8] MT-45 could become a new public health concern, thus, the vigilance is highly recommended in order to monitor and prevent the spread among drug users.

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ERRATUM

The article, Implementation of a collaborative care management program with buprenorphine in primary care: A comparison between opioid-dependent patients and patients with chronic pain using opioids nonmedically, by Joji Suzuki, MD; Michele L. Matthews, PharmD; David Brick, BA; Minh-Thuy Nguyen; Robert N. Jamison, PhD; Andrew L. Ellner, MD, MSc; Lori W. Tishler, MD; Roger D. Weiss, MD published in the May/June 2014 issue of *Journal of Opioid Management*; Volume 10, Number 3, pages 159-168 has an additional author who was not listed.

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